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Chiral Lewis Base-Catalyzed, Enantioselective Reduction of Unprotected β-Enamino Esters with Trichlorosilane

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Abstract: Catalytic asymmetric reduction of N-unsubstituted β-enamino esters represents a major challenge for asymmetric catalysis. In this paper, the first organocatalytic system that could be used for the asymmetric hydrosilylation of N-unsubstituted β-enamino esters has been developed. Using *N-tert*-butylsulfinyl-L-proline-derived amides and L-pipecolinic acid-derived formamides as catalyst, a broad range of β-aryl- and β-alkyl-substituted free β-amino esters could be prepared with high yields and enantioselectivities. The practicality was illustrated by the gram-scale asymmetric synthesis of ethyl (*R*)-3-amino-3-phenylpropanoate and isopropyl (*S*)-3-amino-4-(2,3,5-trifluorophenyl)butanoate. The resulting product can be smoothly transformed to the FDA approved medicines dapoxetine and sitagliptin in a short synthetic route.

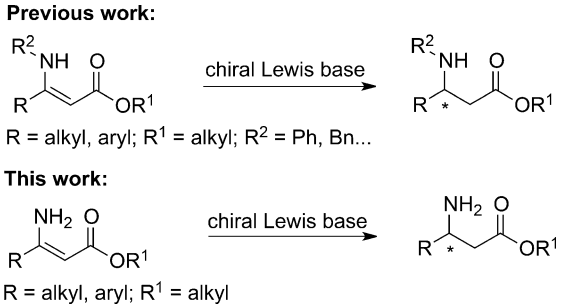
Keywords: β-amino esters; asymmetric hydrosilylation; Lewis bases; reduction; trichlorosilane

Enantiometrically pure β-amino acids and their derivatives are ubiquitous important structural motifs that can be found in a vast number of pharmaceutical and agrochemical substances,[1] such as dapoxetine (treatment of premature ejaculation),[2] ezetimibe (reduction of plasma cholesterol level), sitagliptin (anti-diabetic), and maraviroc (treatment of HIV infection).[3] Therefore, many approaches have been developed for the enantioselective synthesis of chiral β-amino acids,[4] among which the catalytic asymmetric reduction of β-enamino esters represents the most efficient and straightforward one.[5]

In the past decades, transition metal[6] and organic Lewis base[7] catalyzed asymmetric hydrogenation of β-enamines has been certified as a powerful methodology to obtain optically pure amines. Recently, we and others reported a series of organic Lewis bases-catalyzed asymmetric hydrosilylations of β-enamino esters for the preparation of chiral β-amino acids.[8] Despite these advances, however, such reductions have been limited to N-substituted enamines. Herein, we reported the first organocatalyst catalyzed highly enantioselective asymmetric reduction of N-unsubstituted β-enamino esters.

β-Amino acids are attracting increasing attention as chiral building blocks, especially in the pharmaceutical and agrochemical industry. However, despite the fact that the chiral Lewis base-catalyzed asymmetric reduction could be done under mild reaction conditions with cheap and metal-free reagents, this transformation has never been considered as a mainstream technology in this field.[9] The main reason is that the substrate scope of the existing organocatalytic systems was confined to N-substituted enamino esters and the nitrogen substituent group, which is not usually the desired functional group, needs to be removed under often harsh reaction conditions. Thus, developing a generally applicable and highly efficient organocatalytic system for the direct reduction of free β-enamino esters has attracted considerable interest. However, to the best of our knowledge, there are no organocatalytic systems available to date and it thus remains a major challenge.

In 2006, Matsumura and co-workers reported the first example of organocatalytic reduction of free β-enamino esters with trichlorosilane, but only 41% enantiomeric excess could be achieved.[10] At the outset of our work, we hypothesized that the nitrogen atom of the enamino substrate could bound to trichlorosilane to form a complex, and it could be converted to the reduced product under the catalysis of Lewis bases (Scheme 1). The steric hindrance of the catalyst and N-substituent group of the substrate are very important for the enantioselectivity of the reduction system. Owing to the decreased steric hindrance of the free β-enamino esters, a catalyst with more steric hindrance may be required for the asymmetric reductions to achieve high enantioselectivity.

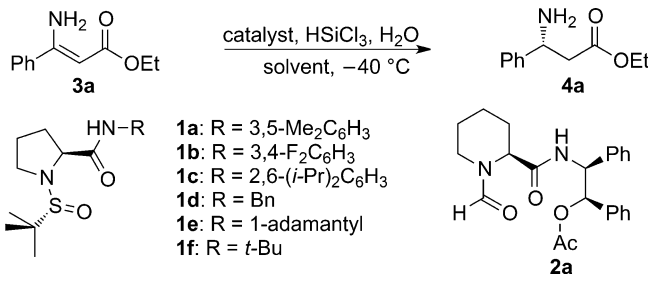


Scheme 1. Strategies for the synthesis of β-amino acids.

Initially, *N-tert*-butylsulfinyl-L-proline-derived amide catalyst **1a** and L-pipecolinic acid-derived formamide **2a** were tested, respectively, in the reduction of β-phenyl β-amino ester **3a** (Table 1, entries 1 and 7). Satisfyingly, the desired product **4a** was obtained with 93% yield and with a high enantiomeric ratio (*er*) of 88.5:11.5 under the catalysis of 10 mol% of **1a**. Catalyst **2a** has a very low catalytic activity under the existing reaction conditions, but a 90.0:10.0 *er* could still be obtained. Encouraged by these results, catalysts **1b–f** were tested. We found that 92.5:7.5 *er* could be obtained when catalysts **1e** and **1f** were used, respectively (Table 1, entries 5 and 6). A 93% yield and 97.0:3.0 *er* could be achieved when 20 mol% of catalyst **1e** was added. After careful investigation, we identified the best reaction conditions in which the reduction of β-phenyl β-enamino ester **3a** is performed using 20 mol% of catalyst **1e**, trichlorosilane (3.0 equiv.), and H_2O (1.0 equiv.) in toluene at −40 °C for 36 h.[11]

With the optimized reaction conditions in hand, the scope of the enantioselective asymmetric reduction of N-unsubstituted β-enamino esters was next investigated (Table 2). A variety of N-unsubstituted β-enamino esters was efficiently reduced to afford the corresponding free β-amino esters with high yields and enantioselectivity. The R^2 group of the β-enamino ester could be replaced with other groups such as methyl, benzyl, cyclohexyl, and isopropyl. High enan-

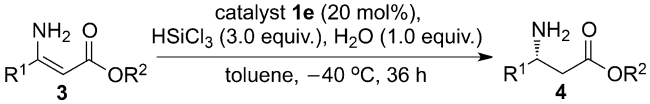
Table 1. Asymmetric hydrosilylation of N-unsubstituted β-phenyl-β-enamino ester **3a** catalyzed by Lewis base catalysts **1a–f** and **2a**.[a]



Entry	Catalyst (mol%)	Solvent	Yield [%][b]	*er*[c,d]
1	**1a** (10)	toluene	93	88.5:11.5
2	**1b** (10)	toluene	73	90.0:10.0
3	**1c** (10)	toluene	85	91.5:8.5
4	**1d** (10)	toluene	80	90.5:9.5
5	**1e** (10)	toluene	80	92.5:7.5
6	**1f** (10)	toluene	88	92.5:7.5
7	**2a** (10)	toluene	7	90.0:10.0
8	**1c** (20)	toluene	90	94.0:6.0
9	**1e** (20)	toluene	93	97.0:3.0
10	**1f** (20)	toluene	88	95.0:5.0
11	**1e** (20)	CCl_4	80	91.0:9.0
12	**1e** (20)	CH_2Cl_2	<5	–
13	**1e** (20)	$CHCl_3$	<5	–
14	**1e** (20)	THF	18	61.0:39.0
15	**1e** (20)	CH_3CN	<5	–
16	**1e** (5)	toluene	70	81.0:19.0

[a] Unless noted otherwise, reactions were performed with **3a** (0.2 mmol), H_2O (0.2 mmol), and $HSiCl_3$ (0.6 mmol) in solvent (2.0 mL) at −40 °C for 36 h.
[b] Isolated yield of **4a**.
[c] The products were derivatized with TsCl and then determined by HPLC with a chiral stationary phase.
[d] Product **4a** obtained from the catalyst **1**-catalyzed reactions was determined to have *R* configuration and the **2a**-catalyzed reaction gave *S* configuration product by comparison of the HPLC data with the literature data.

Table 2. Asymmetric reduction of various unprotected β-enamino esters.[a]



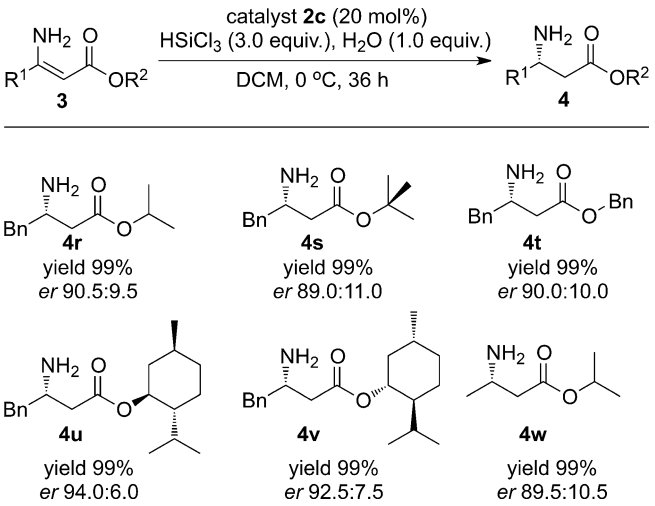
Entry	R^1	R^2		Yield [%][b]	*er*[c]
1	Ph	Et	**4a**	93	97.0:3.0
2	Ph	Me	**4b**	91	94.5:5.5
3	Ph	Bn	**4c**	90	94.0:6.0
4	Ph	Cy	**4d**	91	95.5:4.5
5	Ph	*i*-Pr	**4e**	85	94.0:6.0
6	4-FC_6H_4	Et	**4f**	85	92.5:7.5
7	4-ClC_6H_4	Et	**4g**	93	95.5:4.5
8	3-ClC_6H_4	Et	**4h**	92	91.0:9.0
9	4-BrC_6H_4	Et	**4i**	87	93.5:6.5
10	4-$CF_3C_6H_4$	Et	**4j**	84	95.5:4.5
11	4-MeC_6H_4	Et	**4k**	90	93.5:6.5
12	4-$MeOC_6H_4$	Et	**4l**	88	94.0:6.0
13	3-$MeOC_6H_4$	Et	**4m**	87	95.0:5.0
14	2-naphthyl	Et	**4n**	92	94.5:5.5
15	2-thienyl	Et	**40**	86	91.5:8.5
16	2-furanyl	Et	**4p**	60	85.0:15.0
17	Bn	Et	**4q**	95	60.0:40.0

[a] Unless noted otherwise the reactions were set with catalyst **1e**, substrate **3** (0.2 mmol), H_2O (0.2 mmol), and $HSiCl_3$ (0.6 mmol) in toluene (2.0 mL) at −40 °C for 36 h.
[b] Yield of isolated product.
[c] The products were derivatized with TsCl and then determined by HPLC with a chiral stationary phase.

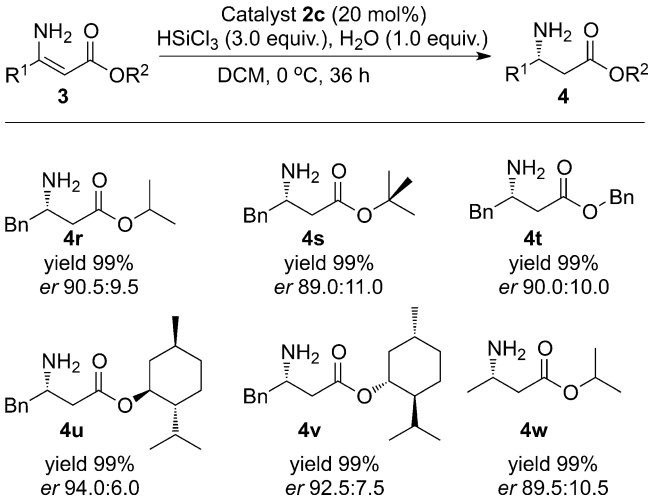
tioselectivities and yields could be obtained when these substrates were reduced in the reaction (Table 2, entries 1–5). Electron-donating and electron-withdrawing substitution at the *para* position of the phenyl ring are well tolerated (Table 2, entries 6–12). When the R^1 group was *p*-tolyl, the substrate could be reduced in 90% yield and with an *er* of 93.5:6.5. When the R^1 was 4-methoxyphenyl, 88% yield and 94.0:6.0 *er* could be obtained (Table 2, entries 11 and 12). When the R^1 groups were electron-withdrawing group substituted phenyls such as 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, and 4-(trifluoromethyl)phenyl, the substrate could also be reduced in high yields and enantioselectivities (Table 2, entries 6, 7, 9 and 10). Electron-donating and electron-withdrawing substitutions at the *meta* position are equally well tolerated. When the R^1 were 3-chlorophenyl and 3-methoxyphenyl, the substrates could be reduced to the corresponding amino esters in high yields and enantioselectivities (Table 2, entries 8 and 13). However, the *ortho* substituted phenyls are not tolerated (see the Supporting Information). Interestingly, we found the R^1 could be other aromatic groups such as naphthalen-2-yl, thiophen-2-yl, and furan-2-yl. These substrates could be reduced to the corresponding amino esters with good to high yields and enantioselectivities (Table 2, entries 14–16).

However, we found the substrate scope of this *N-tert*-butylsulfinyl-L-proline-derived amide catalyst system was limited to β-aryl-β-enamino esters. The β-alkyl-β-enamino esters such as ethyl (*Z*)-3-amino-4-phenylbut-2-enoate **3q** could be reduced by this catalysis system to get the corresponding product with high yield, but poor enantioselectivities were observed (Table 2, entry 17). In order to prepare chiral β-alkyl-β-amino esters, our previously prepared Lewis base catalysts have been rescreened. Using (*Z*)-3-amino-4-phenylbut-2-enoate **3q** as standard substrate, we found it could be reduced with excellent yields and with good enantioselectivities under the catalysis of L-pipecolinic acid-derived formamides (Scheme 2). Formamide **2c**, in which the R group is MOM, was shown to be the best catalyst since **3q** could be reduced in 99% yield and with an *er* of 87.0:13.0.

After careful investigation, we identified the best reaction conditions in which the reduction of (*Z*)-3-amino-4-phenylbut-2-enoate **3q** is performed using 20 mol% of catalyst **2c**, trichlorosilane (3.0 equiv.), and H_2O (1.0 equiv.) in dichloromethane at 0 °C for 36 h. Interestingly, we found 90.5:9.5 *er* could be obtained when the ethyl in **3q** was replaced with isopropyl (**3r**) (Scheme 3). And it could be further improved to 94.0:6.0 when it was replaced with D-menthyl (**3u**). More interestingly, the same major enantiomer was formed in the reduction with an *er* of 92.5:7.5 when it was replaced with L-menthyl (**3v**) (see the Supporting Information).



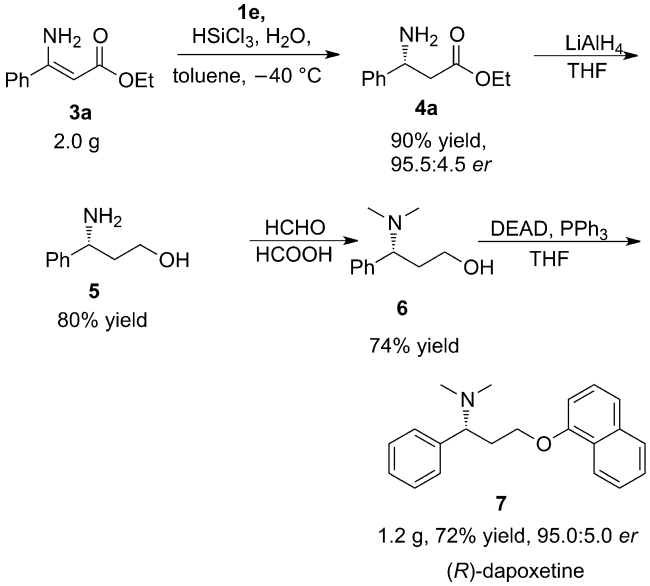
Scheme 2. Formamide-catalyzed asymmetric reduction of (*Z*)-3-amino-4-phenylbut-2-enoate **3q**. The products were derivatized with PhNCS and then determined by HPLC with a chiral stationary phase. Product **4q** has an *S* configuration by comparison of the HPLC data with the literature data. See the Supporting Information for details of the reaction conditions.



Scheme 3. Catalyst **2c**-catalyzed asymmetric reduction of β-enamino esters.

In order to illustrate the synthetic potential of these methodologies, the products of the current catalytic systems have been used to prepare chiral dapoxetine and sitagliptin. As shown in Scheme 4, using the asymmetric reduction product **4a** as a key starting material, dapoxetine could be prepared in four steps by the following procedure with overall 43% yield and 95.0:5.0 *er*.[12]

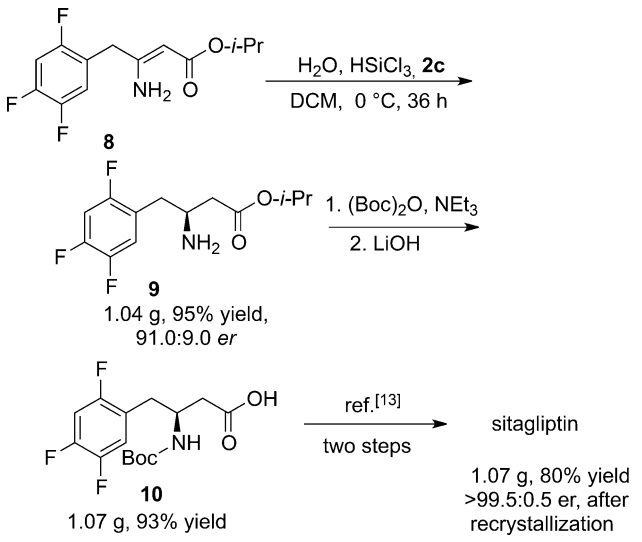
The phosphate salt of sitagliptin has been approved by the US FDA for the management of type 2 diabetes mellitus. Numerous reports on the synthesis of sitagliptin have appeared.[13] However, to the best of our knowledge, an inexpensive reagent-based asym-



Scheme 4. Synthesis of dapoxetine.

metric synthesis of sitagliptin remains unprecedented. Our strategy for the synthesis of chiral sitagliptin was started with 2-(2,4,5-trifluorophenyl)acetic acid (Scheme 5). The β-2,4,5-trifluorophenyl β-enamino ester substrate **8** could be easily prepared in three steps with an overall 84% yield. The substrate **8** could be reduced to the chiral β-2,4,5-trifluorophenyl β-amino ester **9** by the **2c**-catalyzed asymmetric hydrosilylation reaction with 95% yield and 91.0:9.0 *er*.[14] With this key intermediate in hand, sitagliptin could be synthesized in 4 steps by the reported synthetic route with an overall 68% yield and 91.0:9.0 *er*. More importantly, we also found thatr the enantiopurity of the final product could be increased to 99% when it was recrystallized from ethyl acetate and hexane.

In summary, we have developed two useful catalytic systems which could be used to prepare chiral β-aryl-β-amino esters and β-alkyl-β-amino esters, respectively. The *N*-sulfinyl-L-proline amides-catalyzed asymmetric reduction system could be used in the preparation of a broad range of β-aryl-β-amino esters with high yields and high enantioselectivities. The L-pipecolinic acid-derived formamides-catalyzed system could be used to synthesize β-alkyl-β-amino esters, especially β-benzyl-β-amino esters, with excellent yields and with moderate to high enantioselectivities. The synthetic potential of the current methodologies has been proved in the synthesis of (*R*)-dapoxetine and (*S*)-sitagliptin. The full application scope of these catalytic systems and the mechanistic aspects are under exploration and will be reported in due course.



Scheme 5. Asymmetric reduction of β-enamino ester **8** and synthesis of sitagliptin.

Experimental Section

General Procedure for the Catalytic Reduction of β-Enamino Esters

Under an argon atmosphere, trichlorosilane (60 μL, 0.60 mmol) was added dropwise to a stirred solution of β-enamino ester (0.20 mmol), catalyst **1e** or **2c** (0.04 mmol) and water (3.6 μL, 0.20 mmol) in the chosen solvent (2 mL) at the chosen temperature. The mixture was allowed to stir at the same temperature for 36 h. After completion, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The crude product was purified by column chromatography (silica gel, hexane/EtOAc or DCM/MeOH) to afford pure β-amino ester **4**, and then derivatized with TsCl or PhNCS. The *er* values of the dervatives were determined by established HPLC techniques with chiral stationary phases.

Acknowledgements

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